PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 21 DEC 2004
WIPO PCT

Applicant's or agent's file reference TLP/533/PCT1	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IN 02/00207	International filing date *(day/month/year)* 14.10.2002	Priority date *(day/month/year)* 17.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/20		
Applicant THEMIS LABORATORIES PRIVATE LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.11.2003	21.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Rankin, R Telephone No. +31 70 340-4659

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 02/00207

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-3, 5-17	as originally filed
4	received on 15.03.2004 with letter of 12.03.2004

Claims, Numbers

1-31	received on 26.07.2004 with letter of 21.07.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-31
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited Art

Reference is made to the following document:
D1: WO0135941

Amendments

The amendments filed with the letter dated 21st July 2004 meet the requirements of Article 34(2)(b) PCT

Article 33(2) PCT

Claims 1-31 are novel with regard to the prior art (Article 33(2) PCT).

D1 discloses multi layered tablet dosage forms (cf example 25) wherein one layer contains metformin as an active agent (cf examples 1-3) and the other layer contains a thiazolidinedione drug (cf examples 5-7, 9-11). However, the metformin layer is not formulated so as to allow the prolonged release of metformin. Consequently, the subject matter of claims 1-31 is new with regard to D1 (Article 33(2) PCT).

Article 33(3) PCT

Claims 1-31 are inventive with regard to the prior art (Article 33(3) PCT).

The closest prior art is D1.

D1 discloses multi layered tablet dosage forms (cf example 25) wherein one layer contains metformin as an active agent (cf examples 1-3) and the other layer contains a thiazolidinedione drug (cf examples 5-7, 9-11).

The difference between claim 1 and D1 is that in claim 1 the biguanide is formulated in a prolonged release layer whereas in D1 the metformin layer is formulated so as to allow the immediate release of the drug.

The problem may therefore be considered as being to provide a multi layered tablet containing a prolonged release source of biguanide.

Claim 1 solves this problem and is considered inventive (Article 33(3) PCT). This solution is inventive because D1 does not discuss the possibility of producing the biguanide layer as a prolonged release formulation. Furthermore, because of the prolonged release of the biguanide, the formulation of claim 1 has the added technical effect of allowing the drugs to be delivered in a single dosage form which allows the drugs to act synergistically.

Claim 1 is therefore inventive, as are claims 2-31 (Article 33(3) PCT).

PCT Publication No. WO9947128 describes the preparation of Metformin HCl controlled release tablet using biphasic delivery where Metformin HCl is blended with a hydrophilic or hydrophobic polymer to form granules, which are further dispersed or embedded in one or more hydrophilic or hydrophobic polymer or material. However if these biphasic granules are to be used for the preparation of bilayered tablets of Metformin HCl and sulfonyl urea or thiazolidinedione, the size of the tablet becomes relatively large causing inconvenience in swallowing.

Marketed antidiabetic combination preparation is Glucovance RTM, of Bristol Myers Squibb (Physician Desk Reference, Ed.55, Pg. 3477), which comprises of Metformin HCl and Glyburide as a single integral unit immediate release tablet.

Thus there is no prior art that teaches patient-convenient cost effective pharmaceutical compositions and the manufacture of granules containing biguanide capable of being compressed into tablets with pH independent prolonged release of the biguanide. Further the prior art does not teach compositions and manufacture of granules containing biguanide capable of being compressed into bilayered tablets with the other layer comprising of active pharmaceutical ingredients belonging to class of thiazolidinedione, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers for desired layer-selective immediate release of these active pharmaceutical ingredients and pH independent, prolonged in-vitro release of biguanide. The prior art also does not teach compositions and methods of manufacturing of multiplayer tablets with such characteristics.

Objects of the invention:

The object of the invention is to provide process for the manufacture of patient convenient, cost effective antihyperglycemic pharmaceutical compositions in multi-layered tablet dosage form capable of layer-selective prolonged release of one active pharmaceutical ingredient(s) in the group of biguanides and layer-selective of immediate release of another active pharmaceutical ingredients belonging to the group of thiazolidinediones, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers.

CLAIMS.

We claim:

1. A process for the manufacture of multi-layered tablet dosage of antihyperglycemic pharmaceutical compositions for once a day administration comprising
   a) preparing the novel granules formulation containing the biguanide or its pharmaceutically acceptable salts which is to be "prolonged released"
   b) preparing the novel granules formulation containing the active pharmaceutical ingredients (API) or their pharmaceutically acceptable salts to be 'immediate released";
   c) screening and sizing the prepared granules ;
   d) treating the screened and sized granules with lubricants ; and
   e) compressing the granules to create the tablets containing the layers as desired.
2. The process as claimed in claim 1 wherein the group of biguanides used are Metformin, Buformin and Phenformin and their Pharmaceutical acceptable salts such as Metformin HCl.
3. The process as claimed in claim 1 wherein the APIs used in claim 1 belong to the group of thiazolidinediones, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers.
4. A process for the manufacture of composition as claimed in claim 1 wherein layer-selective immediate release of thiazolidinediones where the said thiazolidinediones is but not limited to Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts thereof such as Pioglitazone HCl and are present in amount from about 5% to about 30% by weight of the corresponding layer.
5. A process as claimed in claim 1 wherein
   a. The biguanide e.g. Metformin HCl is pulverized to particle size of less than 100 microns or less and it comprises atleast 48% and preferably over 50% of the formulation composition.
   b. Metformin HCl is blended with non-biodegradable, inert polymer, blending carried out in mixers such as planetary mixers, octagonal blenders, V-blenders or rapid mixer granulators or fluid bed granulators.

c. the API-polymer blend is wet granulated using a solvent optionally containing binders and plasticizers, in the presence of a granulation solvent being water or hydroalcoholic solution.

d. The granulated mass is dried followed by sizing using comminuting mill such as Fitz mill or oscillating granulator or any other equipment suitable for the purpose, with an appropriate mesh preferably around 1-mm mesh.

e. the granules thus produced are mixed with Talc, magnesium stearate and colloidal silicon dioxide.

6. A process as claimed in claim 1 wherein :
   - The particle size of Pioglitazone HCl used is less than 30 microns.
   - the pioglitazone HCl is blended with fillers, disintegrants, binders, lubricants and permitted colours carried out in planetary mixer, octagonal blender, double cone blender, rotary mixer granulator, drum mixer, ribbon blender, fluid bed processor or any other suitable mixer.
7. A process as claimed in claim 5, wherein the non-biodegradable, inert polymers are selected from the group consisting of cellulose derivatives, (meth)acrylic acid co-polymers, Xanthan gum, Guar gum, Alginates and their acceptable salt thereof.
8. A process as claimed in claim 7, wherein the non-biodegradable, inert polymers are selected from a minimum of one or more cellulose derivative or combination of cellulose derivatives with (meth)acrylic acid co-polymers or combination of cellulose derivatives with alginates and /or (meth)acrylic acid co-polymers or combination of cellulose derivatives with Xanthan gum or combination of cellulose derivatives with guar gum.
9. A process as claimed in claim 7- 8, wherein the cellulose derivative is alkylcellulose and/or hydroxyalkylcellulose and/or carboxyalkylcellulose, the (meth)acrylic acid co-polymers are selected from esters of ethyl acrylate and methyl methacrylate, ethyl ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers methacrylic acid and methyl methacrylate copolymers , alginate and their acceptable sodium and calcium salt.

10. A process for the manufacture of the compositions as claimed in claims 1,5,7 - 9 wherein the cellulose derivatives are selected from methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose are incorporated in amount of at least 35% by weight of the biguanide more preferably 40-65 % by weight of the biguanide.
11. A process as claimed in claims 1, 5, 7 - 10 wherein the binary combinations of the polymers are selected from combinations of hydroxypropylmethylcellulose and hydroxypropylcellulose; hydroxypropylmethylcellulose and hydroxyethylcellulose; hydroxypropylmethylcellulose and sodium carboxymethylcellulose; hydroxypropylmethylcellulose and sodium alginate; hydroxypropylmethylcellulose and Xanthan gum ; hydroxypropylmethylcellulose and guar gum; in the ratios ranging from about 1 : 0.01 to about 1 : 3.5.
12. A process as claimed in claims 1, 5, 7 - 10 wherein a combination of three polymers hydroxypropylmethylcellulose, sodium carboxymethylcellulose and methacrylic acid copolymer is used in ratios of about 1 : 0.01: 0.1 to about 1 : 3.5 : 0.5 respectively.
13. A process as claimed in claims 1, 5, 7 - 12 wherein the polymers used is at least 35% by weight of the biguanide most preferably 40-65 % by weight of the biguanide.
14. A process as claimed in claims 1, 5, 7 – 13 for the preparation of the antihyperglycemic pharmaceutical compositions in multi-layered/bi-layered tablet wherein the nominal viscosity at 20°C of a 2% w/w aqueous solution of hydroxypropylmethylcellulose used is not less than 3000cP, the nominal viscosity of a 1%w/w aqueous solution of Sodium alginate at 20°C is not less than 50cP and the nominal viscosity of a 1%w/w aqueous dispersion of guar gum is not less than 2000 cP.
15. A process as claimed in claims 1, 5, 7 - 13, wherein for the preparation of the antihyperglycemic pharmaceutical compositions in multi-layered/bi-layered tablet wherein the nominal viscosity at 25°C of a 1% w/w aqueous solution of hydroxypropylcellulose is not less than 1500cP; hydroxyethylcellulose is not less

than 1500cP.; sodium carboxymethylcellulose is not less than 1500 cP and xanthan gum is not less than 1200 cP.

16. A process as claimed in claims 1, 4, 6 wherein the disintegrating agents are selected from the group comprising starch, sodium starch glycollate, crosscarmellose sodium, crosspovidone, pregelatinized starch, microcrystalline cellulose, hydroxypropylcellulose.
17. A process for the composition as claimed in claims 1-6, 16 wherein the immediate release layer containing a combination of thiazolidinediones and biguanides with the exciepients and other formulation ingredients comprises about 5% to about 30% by weight of the thiazolidinediones and about 1 to about 10% of biguanides.
18. A process according to claims 1 - 6 where Metformin HCl is in the range of 500mg -2000mg and Pioglitazone HCl equivalent to Pioglitazone is in the range of 15 - 60 mg.
19. A process according to claims 1, 2, 5 wherein the granules of the biguanide prolonged release layer formed can be stored for prolonged period without change in compression characteristic.
20. A process according to claim 1-19 wherein, the bilayer tablet formed has hardness in the range of about 6 to about 12 kg/ Sq. cm, low friability of <1% without capping.
21. A process for the manufacture of composition as claimed in claims 1-20 wherein the layers of the tablet are parallel to each other.
22. A process for the manufacture of composition as claimed in claims 1-20 wherein one layer is only partially covered by the next layer.
23. A process according to claims 1- 22 wherein, the multilayer tablet is enrobed by soft gelatin ribbons for additional protection against oxidation, photodegradation, identification, ease of swallowing, taste masking and for aesthetic appeal without altering the dissolution profile.
24. A process for manufacture of granules containing biguanide as or its pharmaceutically acceptable salts claimed in claims1, 2, 5, 7 – 15, 18 - 19 capable of being compressed to a tablet dosage form with pH independent prolonged release of biguanide at the end of 1, 4, and 8 hours lies in the range of 25 – 45%, 50 – 80% and not less than 75% respectively.

process for manufacture of granules containing active pharmaceutical ingredients (API) or their pharmaceutically acceptable salts claimed in claims 1, 3 – 4, 6, 16, 18 capable of being compressed to a tablet dosage form with immediate release of the same is not less than 80 % at the end of 30 minutes.

26. A pharmaceutical compositions in multi-layered tablet dosage form capable of layer-selective prolonged release of one active pharmaceutical ingredient (API) or APIs in the group of biguanides and layer-selective of immediate release of another API or APIs belonging to the group of thiazolidinediones, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers.
27. A pharmaceutical composition claimed in claim 26 in which the prolonged release pharmaceutical ingredient belongs to the group of biguanides and the intermediate release active pharmaceutical ingredient belongs to the group of thiazolidinediones and/or biguanides.
28. A composition as claimed in claim 26-27 wherein the immediate release API or APIs are present in an amount of from 5%-30% by wt..
29. A composition as claimed in claims 26-28 wherein the immediate release layer containing a combination of thiazolidinediones and biguanides with the exciepients and other formulation ingredients comprises about 5% to about 30% by weight of the thiazolidinediones and about 1 to about 10% of biguanides.
30. A composition as claimed in claims 26-29 capable of layer-selective prolonged release of biguanides where the said biguanides is but not limited to Metformin, Buformin and Phenformin and their Pharmaceutical acceptable salts such as Metformin HCl.
31. A composition as claimed in any one of claims 26-30 wherein layer-selective immediate release of thiazolidinediones where the said thiazolidinediones is but not limited to Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts thereof such as Pioglitazone HCl.
32. A composition as claimed in claims 26-31, wherein the prolonged release layer contain Metformin HCl and the immediate release layer contain Pioglitazone HCl.